Review Article

Inhaled insulin: A "puff" than a "shot" before meals

Dick B. S. Brashier, Anjan Khadka[1], Tejus Anantharamu, Ashok Kumar Sharma, A. K. Gupta, Sushil Sharma, N. Dahiya

Department of Pharmacology, Armed Forces Medical College, Pune, Maharashtra, India, [1]Department of Pharmacology, Nepalese Army Institute of Health Sciences, Kathmandu, Nepal

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ABSTRACT

Diabetes is a metabolic disorder characterized by relative or absolute deficiency of insulin, resulting in hyperglycemia. The main treatment of diabetes relies on subcutaneous insulin administration by injection or continuous infusion to control glucose levels, besides oral hypoglycemic agents for type 2 diabetes. Novel routes of insulin administration are an area of research in the diabetes field as insulin injection therapy is burdensome and painful for many patients. Inhalational insulin is a potential alternative to subcutaneous insulin in the management of diabetes. The large surface area, good vascularization, immense capacity for solute exchange and ultra-thinness of the alveolar epithelium facilitates systemic delivery of insulin via pulmonary administration. Inhaled insulin has been recently approved by Food and Drug Administration (FDA). It is a novel, rapid-acting inhaled insulin with a pharmacokinetic profile that is different from all other insulin products and comparatively safer than the previous failed inhaled insulin (Exubera).

Key words: Diabetes, inhaled, insulin, nasal spray

INTRODUCTION

Diabetes is one of the greatest challenges in medical field affecting 347 million people worldwide. It is projected to be the seventh leading cause of death by 2030 and >80% deaths due to diabetes occur in low- and middle-income countries.[1] Diabetes mellitus (DM) is described by WHO as a metabolic disorder of multiple etiology, characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action or both; the effects of which include long-term damage, dysfunction and failure of various organs.[2]

The goals of therapy for diabetes are to alleviate the symptoms related to hyperglycemia and to prevent or reduce the acute and chronic complications of diabetes. Insulin is the mainstay for treatment of virtually all type 1 and many type 2 diabetes patients though there is a long list of glucose-lowering agents like sulphonylureas, biguanides, thiazolidinediones, glucagon-like peptide analogs, dipeptidyl peptidase-IV inhibitors, amylin analogues, alpha glucosidase inhibitors etc.[3]

Insulin is regarded as the first choice in case of type 2 DM, particularly in thin individuals or those with severe weight

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Address for correspondence:
Anjan Khadka, Department of Pharmacology, Nepalese Army Institute of Health Sciences (NAIHS), Kathmandu, Nepal.
E-mail: anjankhadka14@yahoo.com

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loss, in individuals with underlying renal or hepatic disease that precludes oral glucose-lowering agents, or in hospitalized or acutely ill individuals. Insulin therapy is ultimately required by almost all individuals with type 2 DM because of the progressive nature of the disorder and the relative insulin deficiency that develops in patients with long-standing diabetes.[4]

Insulin may be administered intravenously, intramuscularly, or subcutaneously. The major drawback of currently available formulations of insulin is that they have to be injected and moreover fail to mimic physiological postprandial insulin delivery into systemic circulation.[5] There have been continuous efforts to find new insulin formulations and new routes of administration so that it mimics physiological secretion of pancreatic beta-cells.[6] Oral insulin is currently being studied in type 1 diabetes prevention with promising results and inhalational insulin has been recently approved by Food and Drug Administration (FDA) on 27 June 2014 for glycemic control in adults with type 1 and type 2 DM.[7-9]

Inhalational insulin has been developed by MannKind Corporation and it is a novel rapid-acting inhaled insulin available as "Afrezza" with a drug device in the form of small easy to use inhaler and the inhalational powder as single-use cartridges.[9] The idea of making inhalation as the route of delivering insulin is not entirely new; seven years ago when Exubera (Pfizer Inc's) received FDA approval it was thought to be a great achievement, but quickly faded out as concerns were raised about its safety regarding its effect on lung function, its heavy price tag and bulky inhaler.[10]

Various strategies are being worked out to reduce the gap between physiological and non-physiological insulin release so as to reduce the complications. Pulmonary route of insulin delivery appears to be a feasible option to enhance this synchronization as lungs with thin epithelium, rich blood supply and a vast absorbing surface help in rapid absorption of insulin delivered to it.[5,11-14]

ISSUE WITH PULMONARY DELIVERY OF INSULIN

The idea of pulmonary delivery of insulin has passed various hurdles. All the below-mentioned factors favor inhaled insulin (Afrezza) than the earlier version Exubera.[5,13,14]

- The preparation of freeze-dried powder insulin in a stable form of micro particles (Bis-3, 6 (4-fumarylaminobutyl)-2, 5-diketopiperazine or FDKP) as excipient which translates into microcrystalline plates under slightly acidic conditions onto which insulin can be adsorbed. FDKP is an inert excipient and is absorbed but not metabolized and will be excreted via urine
- These particles have an average diameter of 2.5 μm, with >90% being in range of 0.5-5.8 μm (suitable for inhalation as will be delivered into alveoli without hindrance)
- The high solubility of these particles at pH >6 matches with the prevailing physiological pH in lungs that helps in easy dissolution and absorption into systemic circulation.

PHARMACOKINETICS

It is ultra-rapid-acting insulin which mimics a linear dose-related pharmacokinetic profile in patients of type 1 and 2 DM.[13] Maximum plasma drug concentration reached between 10 and 15 min (T_{max}) which is very early compared to regular insulin or other rapidly acting insulin analogues (20-45 min). This is important as it mimics first-phase insulin release after food seen in non-diabetic individuals. Duration of action is around 2-3 hrs.[13-15] 60% of the inhaled drugs gets deposited in the lungs.[14] Inhaled insulin is designed to be used within 20 min of beginning a meal [Figure 1].

DEVICE SYSTEM

Breath-powder inhaler is used which can be re-used after changing the cartridge for 15 days. The procedure has been made very simple to enhance the compliance in which the cartridge of powdered insulin is placed, then close the device and with a single breath the powder will be inhaled; later open the device, remove the cartridge out and then discard.[16]

This device offers various advantages:[13,16,17]

- The device is small and easy to carry along
- No need of synchronizing with the inhalation as this device is designed in such a way that it senses and gets activated with inhalation on its own
- Effectively protects the powdered insulin from getting affected by moisture
- Re-usable

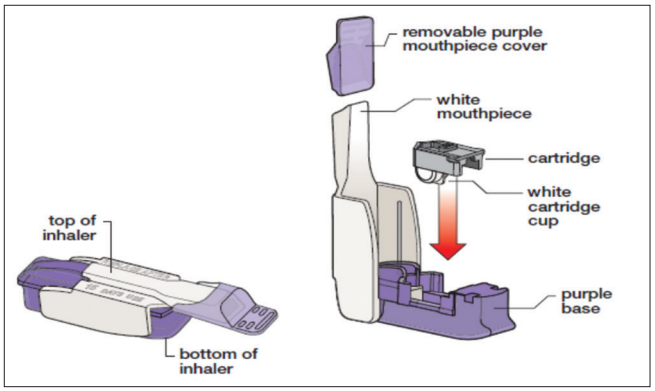

Figure 1: Insulin inhaler[20]

Inhalational insulin system uses "flow balance concept." The powder placed in the cartridge has to be broken up and dispersed (de-agglomerated) before delivery into lungs. The air which flows through the device initiates this process and lifts all the powder in the cartridge to reach the exit port; but there is a by-pass channel carrying air which also reaches the exit port and intersects the air coming from mouthpiece and completes the process of de-agglomeration.[13,14,17,18-20]

Inhalational insulin is available in two strengths [Figures 1 and 2] in foil packages. One foil package consists of two blister cards and there are five strips per blister card. Each strip contains three cartridges. It is administered using a single inhalation per cartridge. Cartridge should be stored at 2-8°C (36-46°F).[13,15,18-20] [Figures 2-4].

CLINICAL EFFICACY

A study showed that the after injecting 60 U of TI (Technosphere insulin = Afrezza) in patients of type 2 DM, the maximal suppression of postprandial endogenous glucose production occurred within 45 min compared to 10 U of SC rapidly acting insulin analogs.[16,17,19,20]

Efficacy and safety data from a clinical trial where in both type 1 (3017 patients) and type 2 (1991 patients) were studied which showed a reduction of HbA1c levels reduction by 0.4% in both groups at the end of 24 weeks. In another 24 week study involving 500 patients of type 1 DM, glycemic control was equal among Afrezza and injected rapidly acting insulin group, but the Afrezza group had less incidence of hypoglycemia probably due to rapid and short duration of action.[20,21]

A 52-week randomized, open-label, parallel –group study evaluating the safety and efficacy of long-acting insulin + prandial TI (Technosphere Insulin) versus a twice daily injection of premixed insulin in patients of type 2 DM showed similar and non-inferior results.[16,17,20]

It is not a substitute for long-acting insulin. It must be used in combination with long-acting insulin in patients with type 1 diabetes, and it is not recommended for the treatment of diabetic ketoacidosis (DKA) as trials suggest an increased incidence of DKA in patients on Afrezza. It is better not to be used in smokers as there is a possible risk of reduction in lung function.[17,20]

ADVERSE EFFECTS

The most common adverse reactions include hypoglycemia, cough, throat pain and irritation. There is some evidence

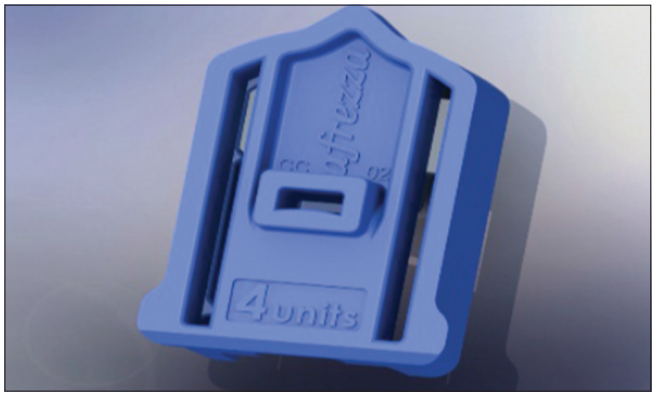

Figure 2: 4 Units inhalational insulin[20]

Injected Mealtime Insulin Dose	AFREZZA® Dose	# of 4 unit (blue) cartridges needed		# of 8 unit (green) cartridges needed
up to 4 units	4 units			
5-8 units	8 units			
9-12 units	12 units		+	
13-16 units	16 units			
17-20 units	20 units		+	
21-24 units	24 units			

Figure 4: Mealtime inhaled insulin (Afrezza) dose conversion table[20]

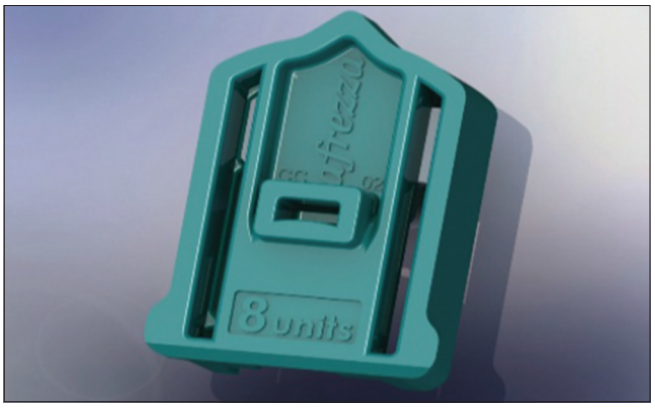

Figure 3: 8 Units inhalational insulin[20]

Figure 5: Insulin (Exubera) inhaler

reduction in FEV_1 of lung function, but overall long-term effects and the need for withdrawal has not yet been established as it is for its predecessor Exubera [Figure 5]. Serious risk includes bronchospasm in patients with asthma, COPD and smokers.[17,20-22]

PRECAUTIONS AND CONTRAINDICATIONS

Precaution should be taken in patients of asthma and COPD and in fluid retention and heart failure. It is contraindicated in hypoglycemia, hypersensitivity to regular human insulin, chronic lung disease such as asthma or COPD, active lung cancer and hypokalemia.[17,20-22]

Pregnancy: Category C.

INDICATIONS

Type 1 and 2 DM: It should be used with regimens that include long acting insulin.[9,20]

CONCLUSION

Inhaled insulin has favorable properties compared to currently available drugs and also its predecessor Exubera. It has reproducible insulin delivery, a rapid and a short duration of action compared to regular insulin and rapidly acting analogs of insulin, closely mimicking physiological insulin. The history does not back it and it has to take on the giants in market whenever it comes who are currently ruling and are the regular choice of masses. It has been approved by the FDA but its commercial potential is far from clear.

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Conflicts of interest
There are no conflicts of interest.

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